Please type a plus sign (+) inside this box → [+]

PTO/SB/21 (6-98)
Approved for use through 09/30/2000. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| **Application Number** | 08/444,934 |
| **Filing Date** | May 22, 1995 |
| **First Named Inventor** | Richard M. Lawn |
| Group Art Unit | 1653 |
| Examiner Name | H. Schnizer |
| Total Number of Pages in This Submission | |
| Attorney Docket Number | MSM 101 CONTC |



**ENCLOSURES** *(check all that apply)*

- [X] Fee Transmittal Form
  - [X] Fee Attached
- [ ] Amendment / Response
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [X] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Additional Enclosure(s) *(please identify below)*:

Remarks

**SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT**

| | |
|---|---|
| Firm or Individual name | Patrea L. Pabst |
| Signature | |
| Date | October 12, 1999 |

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: 10/12/99

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|---|---|---|---|
| Typed or printed name | Jean Hicks | | |
| Signature | Jean Hicks | Date | 10/12/99 |

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AF/1653

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# FEE TRANSMITTAL for FY 1999

*Patent fees are subject to annual revision.*
*Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12.*

**TOTAL AMOUNT OF PAYMENT** ($) 680.00

| Complete if Known | |
|---|---|
| Application Number | 08/444,934 |
| Filing Date | May 22, 1995 |
| First Named Inventor | Richard M. Lawn |
| Examiner Name | H. Schnizer |
| Group / Art Unit | 1653 |
| Attorney Docket No. | MSM 101CONT |

OIPE OCT 14 1999 JC42 PATENT & TRADEMARK OFFICE

## METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 01-2507

Deposit Account Name: Arnall Golden & Gregory, LLP

[X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

2. [X] **Payment Enclosed:** [X] Check [ ] Money Order [ ] Other

## FEE CALCULATION

### 1. BASIC FILING FEE

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 101 | 760 | 201 | 380 | Utility filing fee | |
| 106 | 310 | 206 | 155 | Design filing fee | |
| 107 | 480 | 207 | 240 | Plant filing fee | |
| 108 | 760 | 208 | 380 | Reissue filing fee | |
| 114 | 150 | 214 | 75 | Provisional filing fee | |

SUBTOTAL (1) ($)

### 2. EXTRA CLAIM FEES

| | Extra Claims | | Fee from below | Fee Paid |
|---|---|---|---|---|
| Total Claims | -20 = | X | | |
| Independent Claims | -3 = | X | | |
| Multiple Dependent | | | | |

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 103 | 18 | 203 | 9 | Claims in excess of 20 |
| 102 | 78 | 202 | 39 | Independent claims in excess of 3 |
| 104 | 260 | 204 | 130 | Multiple dependent claim, if not paid |
| 109 | 78 | 209 | 39 | ** Reissue independent claims over original patent |
| 110 | 18 | 210 | 9 | ** Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) ($)

## FEE CALCULATION (continued)

### 3. ADDITIONAL FEES

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 105 | 130 | 205 | 65 | Surcharge - late filing fee or oath | |
| 127 | 50 | 227 | 25 | Surcharge - late provisional filing fee or cover sheet. | |
| 139 | 130 | 139 | 130 | Non-English specification | |
| 147 | 2,520 | 147 | 2,520 | For filing a request for reexamination | |
| 112 | 920* | 112 | 920* | Requesting publication of SIR prior to Examiner action | |
| 113 | 1,840* | 113 | 1,840* | Requesting publication of SIR after Examiner action | |
| 115 | 110 | 215 | 55 | Extension for reply within first month | |
| 116 | 380 | 216 | 190 | Extension for reply within second month | 380.00 |
| 117 | 870 | 217 | 435 | Extension for reply within third month | |
| 118 | 1,360 | 218 | 680 | Extension for reply within fourth month | |
| 128 | 1,850 | 228 | 925 | Extension for reply within fifth month | |
| 119 | 300 | 219 | 150 | Notice of Appeal | |
| 120 | 300 | 220 | 150 | Filing a brief in support of an appeal | 300.00 |
| 121 | 260 | 221 | 130 | Request for oral hearing | |
| 138 | 1,510 | 138 | 1,510 | Petition to institute a public use proceeding | |
| 140 | 110 | 240 | 55 | Petition to revive - unavoidable | |
| 141 | 1,210 | 241 | 605 | Petition to revive - unintentional | |
| 142 | 1,210 | 242 | 605 | Utility issue fee (or reissue) | |
| 143 | 430 | 243 | 215 | Design issue fee | |
| 144 | 580 | 244 | 290 | Plant issue fee | |
| 122 | 130 | 122 | 130 | Petitions to the Commissioner | |
| 123 | 50 | 123 | 50 | Petitions related to provisional applications | |
| 126 | 240 | 126 | 240 | Submission of Information Disclosure Stmt | |
| 581 | 40 | 581 | 40 | Recording each patent assignment per property (times number of properties) | |
| 146 | 760 | 246 | 380 | Filing a submission after final rejection (37 CFR 1.129(a)) | |
| 149 | 760 | 249 | 380 | For each additional invention to be examined (37 CFR 1.129(b)) | |

Other fee (specify) _____

**Represents the difference between the fee for a [ ] month extension of time and a [ ] month extension of time.

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)680.00

| SUBMITTED BY | | | | Complete (if applicable) | |
|---|---|---|---|---|---|
| Typed or Printed Name | Patrea L. Pabst | | | Reg. Number | 31,284 |
| Signature | | Date | 10/12/99 | Deposit Account User ID | 01-2507 |

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*international

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EUROPEAN PATENT OFFICE
General Direction 2
Erhardstrasse 27
80298 MUNICH - GERMANY

Considered
HS 12-22-99

Your ref.
Our ref. 8E.117.JPR.MJR

Paris, 23 February 1998


SENT BY FAX. CONFIRMATION BY REGISTERED POST

Subject: OBJECTION to EUROPEAN PATENT No. 88 301 190.0/
EPB 0 278 776
In the name of GENENTECH INC.
Objector: DIAGNOSTICA STAGO

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Dear Sirs

In the name of and on behalf of the company DIAGNOSTICA STAGO, we object to the European Patent mentioned above, the granting of which was published in the European Patent Bulletin on 28.05.1997, in accordance with articles 99 ff. of the EPA.

We enclose with this letter:

- a report arguing in favour of revocation of the patent, *(2 copies)*
- a copy of additional documents in support of the report, *(2 copies)*
- proof of payment of the objection fee.

Yours faithfully

Attorney

*(signature)*

Jean-Pierre ROBERT

Encs.

tissues but at low levels of expression. For this type of gene, cloning cDNA is traditionally the first stage in isolation operations. On the basis of a specific example (the hIGF-1 gene), DS7 therefore deals with a problem that is similar to that of the invention that is the subject of the disputed European patent, as is referred to in the description of EP-B-0278776 page 3 lines 17 - 21 and 28 - 30.

Document DS8 is referred to as an additional illustration because it shows that the technique of cloning by hybridisation of oligo-nucleotide probes had been known and mastered for several years in accordance with the same principle and by making use of methods of operation that differ at some points. The oligo-nucleotide probes used by DS8 are shorter (15 - 19 oligo-nucleotides) than those in the disputed European patent EP-B-0278776.

Moreover, with regard to publications later than 12 February 1987, it is clear that several teams of researchers have used the technique of cloning by hybridisation of an oligo-nucleotide probe with success and without difficulty (i) to sequence hTF from a fragment of DNA that codes for the said protein, and then (ii) to express the said protein. They are specifically:

- researchers associated with the holder, namely Karen L FISHER et al, see DS4;
- James H MORRISSEY et al, see DS3 and the document of patent US-A-5110730;
- Eleanor K SPICER (who was part of the team of Yale NEMERSON and William H KONIGSBERG) et al, see DS5 and the document of patent WO-A-88/09817; and
- Eleonora SCARPATI et al, see DS6.

Finally, document DS 9 is referred to in relation to claim 12 of the disputed European Patent EP-B-0278776 which considers the deletion of the transmembrane domain. DS9 does indeed teach (see page 205, right column first sentence of the section "(a) Crystallization") the separation of the extracellular domain in order to obtain (in the case of the HLA molecule) a portion of hydrosoluble protein (i) preserving the biological activity of the complete mature protein but (ii) without the transmembrane and cytoplasmic domains.

***THE CLAIMS OF THE DISPUTED PATENT***

European Patent EP-B-0278776 comprises 26 claims arranged as follows.

- An independent claim 1,

which considers as products (i) the polynucleotide as in figure 2 coding for a particular protein, tissue factor [abbreviated as TF, specifically human tissue factor (abbreviated as hTF)], and (ii) its variants which code for TF or for a variant or fragment deriving from TF by selective insertion, deletion or substitution of at least one amino acid, and

to which the dependent claims 2 and 3 are attached.

In other words claim 1 concerns a polynucleotide defined by its sequence and which codes for a protein, namely hTF, on the one hand, and of variants of the said polynucleotide each defined by the sequence of a different protein of hTF and which each code for the said protein that it is desired to express.

- Independent claims 4 and 6,

which consider a process of preparation, in accordance with a traditional technique of genetic engineering, one of TF, its variants or its fragments, and the other of the said variants or fragments, and

to which the dependent claims 5 and 8, and 7 and 8 respectively are attached.

- Independent claims 9, 10, 11, 12, 13, 16, 17 and 18,

which consider biologically active TF, its variants or its fragments (claim 9) or the said biologically active variants or fragments (claims 10, 11, 12, 13, 16, 17 and 18),

the dependent claims 14, 15 and 19 respectively being attached to claims 13 and 16 respectively.

Claims 10, 11, 12, 13, 16, 17 and 18 should not be considered as independent claims but rather as claims dependent on claim 9.

The technical problem posed was to determine the sequence of hTF for the purpose of producing this protein in useful quantities by recombinant techniques on the one hand, and on the other hand to work out the sequences of the variants and fragments from the said sequence for the purpose of producing them by the same techniques (see page 3 lines 16 - 30).

The solution adopted to solve this technical problem makes use of a traditional technique known to a person skilled in the art.

3.2 The subject of claim 1 is without inventive activity because disclosure DS1 (or the combination of DS1 and DS2) supplied the peptides P1 and P2 before 12 February, the date of the first American priority, and the person skilled in the art therefore had the required elements available to determine the sequence of hTF and then those of its variants and other fragments by simple and routine experiments (even if they were tedious and laborious) with the required chances of success.

3.3 Moreover, in accordance with decision T 386/94 (OJ EPO 1996 658) relating to European Patent 82201272.0/EP-B-0077109 which states:

*"An inventive activity can be recognised in the area of genetic engineering if it is not possible to carry out cloning and expression of a given gene with a reasonable chance of success. However, in the case where at the priority date the person skilled in the art can hope to carry out cloning and expression of the said gene in a relatively simple manner, and the cloning and expression, although they may require a great amount of work, do not pose such difficulties that the hopes of success prove to be illusory, the inventive activity cannot be recognised."*

it was certain in this particular case that the person skilled in the art had no doubt that by combining DS1 (or the combination of DS1 and DS2) with DS7 (or the combination of DS7 and DS8) he would achieve *in fine* the sequencing of hTF with oligo-nucleotide probes constructed from P1 and/or P2.

3.4 The technique of hybridisation of an oligo-nucleotide probe with a cDNA of tissue containing hTF, selection of a product of hybridisation followed by sequencing of the corresponding gene in order to deduce the sequence of the desired protein was indeed fully known before 12 February 1987.

For example, in decision T 386/94 mentioned above and decision T 923/92 (OJ EPO 1996 564) which relates to European Patent 83302501.8/EP-B-0093619, the appeals tribunal 3.3.4 had already had occasion to note that the methodology mentioned above (oligo-nucleotide probe / hybridisation with cDNA / selection of a product of hybridisation / sequencing of the gene in question / deduction of the sequence of the desired protein) constituted a well known process in the area of sequencing proteins.

In addition, some teams of researchers, independently of the co-inventors of the invention that is the subject of the disputed European Patent EP-B-0278776, have applied this methodology without effort in order to achieve sequencing of hTF. This is plainly evident from documents DS3, DS5 and DS6.

3.5 Moreover, it is of little importance that the holder has stated that the cDNA from placental tissue that he was using was unsuitable once he had achieved what he wanted with cDNA from adipose tissue. It is appropriate to make two comments on this matter. The first comment concerns the fact that the holder resorted to a fragment of P1, namely a peptide of 20 amino acids and close to the N-terminal extremity (region 12 - 31 of hTF) and to peptide P2 of 27 amino acids and close to the C-terminal extremity (region 210 - 236 of hTF), in order to construct oligo-nucleotide probes (see page 10, lines 36 - 53 on the one hand and page 11 line 44 to page 12 line 8 on the other hand). The second comment lies in the fact that the holder, who in the course of proceedings on his European Patent insisted on the choice of adipose tissue as the source of cDNA, trace a relationship of equivalence between "placental, adipose and other tissues" in the description of his patent (see page 7 lines 9 - 10) among the tissues of the gene bank containing the said cDNA; because of this relationship of equivalence the selection of an adipose tissue presents no unexpected property and does not confer patentability.

3.6 Once the person skilled in the art has determined the sequence of hTF he has no difficulty in obtaining variants or fragments of this protein. These variants or fragments can be obtained (i) if necessary by enzymatic slicing, particularly to separate the transmembrane and cytoplasm domains in accordance with

DS9, and (ii) in particular by genetic engineering (recombinant process) after having constructed and inserted the portions of DNA into an expression vector, encoding each one for the variant or fragment in question.

4. *Concerning the insufficiency of description*

4.1 TF, particularly hTF, has several activities. The holder states that TF is a "trigger" that can initiate blood clotting in association with phospholipids (see page 2 lines 37 - 39), is a coagulant in the presence of lipids (see page 2 lines 56 - 57), corrects haemostatic deficiencies (see page 3 line 45), corrects bleeding diasthesis (see page 3 line 46; as the term diasthesis is particularly vague in that it encompasses a combination of different conditions that affect the same subject simultaneously or successively and are considered to be of a comparable nature), and is useful in the treatment of various chronic bleeding disorders (see page 3 line 51 to page 4 line 2) and in other uses (see page 4 line 3).

In his description the holder further mentions the use of variants or fragments derived from TF which do not cause coagulation as immunogenic or antagonistic agents of TF and as agents that modify the pharmacological properties of the drug (see page 7 lines 14 - 32).

In consequence the subject of claim 1 is not patentable because of the insufficiency of the description, as the conditions referred to in articles 83 and/or 84 EPA are not satisfied, in that the said claim 1 does not make use of a single precise biological activity of TF, its variants and its fragments as stipulated in the decision T 923/92 mentioned above.

4.2 Claim 1 includes a difficulty with regard to the definition of the variants or fragments of TF. The description does indeed give specific details regarding the variants and fragments of TF. They comprise (i) the different allelomorphs, (ii) the products of three different classes capable of being generated *in vitro* by selective insertion, suppression (deletion) or substitution of at least one amino acid, and (iii) the products resulting from combinations of the said classes.

The substitution variants are products in which an amino acid of TF is replaced by another amino acid (see page 5 line 56).

The insertions are of the order of 1 to 10 amino acids. They are preferably carried out in pairs: they can also concern fusions at the N-terminal and C-terminal extremities; proteins from fusions are considered as insertion variants (see page 5 lines 34 - 39 and lines 56 - 57).

Deletions relate preferentially to peptide fragments of 2 to 6 amino acids. They can be larger (1 to 30 amino acids) when they concern the signal peptide (residues -31 to -1 with preservation of the Met residue from the initial position -32) or the transmembrane domain (residues 220 to 242).

Now it is apparent that the description does not indicate which are the variants that preserve the precise biological activity of TF (which is not referred to in point 4.1 above). As a result, the person skilled in the art, who is able to synthesise any variant or fragment of TF based on his knowledge of the sequence of TF, cannot know in advance whether the product that he expects to obtain or that he has obtained presents a biological activity before he has tested the product.

In other words, the wording of claim 1 really only constitutes a note directed to third parties by which the holder claims "you synthesise a product, and if it is active it belongs to me because it is included in my domain of protection, and if it is inactive it is yours because it is not included in my domain of protection!!"

As a result, the description does not provide the person skilled in the art with sufficient information to enable him to distinguish and select those that are truly active out of all the possible variants and fragments.

As the disputed European Patent EP-B-0278776 is silent on this subject, the comments of the appeals tribunal 3.3.4 in decision T 923/92 mentioned above:

*"If the description contains sufficient information on how to obtain human t-PA and if the claim relating to derivatives of human t-PA indicates the functions to be tested, it must be considered that the person skilled*